History, Philosophy, the Present and the Future(?) of Randomized Controlled Clinical Trials (RCTs)

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Introduction

- What is a clinical trial? A medical experiment?
  - A study to establish the relative efficacy or effectiveness of treatments for patients to facilitate good medical practice and medical policy.
  - Nazi experiments? Tuskegee?

History of Clinical Trials

- Book of Daniel, 12? Limes to prevent scurvy in the British Royal Navy (1600).
- 1900–1915: Direct generalization from bench to bedside.
- 1915–1935: Clinical observation
- 1935 on: Randomized Controlled Clinical Trails (RCTs)

Roots of the RCT

- Previous experience in clinical trials.
- Issues related to causal inferences.
  - "Inference": drawing conclusions to a population from a sample.
- Statistical hypothesis testing
- Ethical Issues
  - "Samaritan" versus "Scientific" ethic
  - "Do No Harm!"

Causality–1

- To show that T causes O, one needs to show that T precedes O (easy!), T is correlated with O (easy!), and that there is no alternative explanation for the association between T and O (!!!).

Causality–2

- The causal effect of T on O for an individual subject is the response of that subject if given T compared to the response of the subject not given T.
- This is always a comparative judgment requiring some definition of what is meant by "not given T": Control or comparison treatment.
- RCT Rule 1: You always need a control or comparison treatment against which T is assessed: C.
- RCT Rule 2: T and C protocols should be well–

Causality–3

- Since you can't both give and not give T to a subject at the same time, not feasible to estimate the causal effect on an individual subject.
- Ah! Can, however, estimate the average causal effect on subjects in a population, by drawing two random samples from the same population, giving T to one, and C to the other.
- RCT Rule 3: You need to sample a specific population of subjects.
- RCT Rule 4: You must randomly assign those subjects to T or C.

Causality–4

- Must measure same O for both T and C.
- Hard, objective measures are fine: e.g. death! Soft, subjective measures are often biased by knowledge of whether a particular patient is getting T or C.
- RCT Rule 5: Must have an a priori specified outcome measure.
- RCT Rule 6: Objective or blinded measures are required, or some protection against bias.

RCT “rules” summary

- Define the protocols for T and C.
- Define the population, and sample it.
- Define a response and how to measure it.
- Randomize the sample to T and C.
- Control for bias by ensuring objectivity or blindness.
- A priori rule as to what “proves” that T is better than C.

Problems with the “rules”

- What is the appropriate control or comparison?
- When is a placebo control ethical?
- What is the appropriate population?
- Biased sample; overgeneralization.
- Dropping subjects after randomization
  - Analysis “by intention to treat”.

More problems with the "rules"

- Efficacy versus Effectiveness
- Multiple Responses
- Post Hoc Responses
- Poorly measured Responses
- What if you can't blind and don't have objective measures?
- What if you can't randomize?
- "You can't fix by analysis what you muddle by design." Light et al

Conclusion

RCTs are the "gold standard" of evaluation of efficacy or effectiveness.

The "rules" are strategies that have evolved over a century, reacting to repeated errors.

If you choose to flout the rules, be prepared for the consequences!